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Chapter

Clinical Manifestations of Giant Cell Arteritis

Ryan Costa Silva, Inês Silva, Joana Rodrigues Santos, Tania Vassalo, Joana Rosa Martins and Ligia Peixoto

Abstract

Giant cell arteritis (GCA), also known as temporal arteritis or Horton disease, is categorized as a large- and medium-sized vessels vasculitis. Systemic symptoms are common in GCA and although vascular involvement may be widespread, the cranial branches of the aortic arch are responsible for the hallmark symptoms of GCA: headache, jaw claudication and ocular symptoms, particularly visual loss. The large vessel (LV)-GCA phenotype may differ or overlap from cranial arteritis. Clinical consequences of LV-GCA comprise aneurysms and dissections of the aorta, as well as stenosis, occlusion and ectasia of large arteries. Symptoms of polymyalgia rheumatica occurring in a patient with GCA include characteristic proximal polyarthralgias and myalgias, sometimes accompanied by remitting seronegative symmetrical synovitis with pitting edema (RS3PE), Less common manifestations reported include central nervous system involvement, audiovestibular and upper respiratory symptoms, pericarditis, mesenteric ischemia and female genital tract involvement.

Keywords: systemic symptoms, cranial arteritis, headaches, visual disturbance, vision loss, polymyalgia rheumatica, RS3PE, large vessel phenotype

1. Introduction

Giant cell arteritis (GCA), also known as temporal arteritis or Horton disease, is a systemic inflammatory large-vessel vasculitis that usually affects the aorta and its major branches [1].

The pathophysiology of GCA is complex and not fully understood. Histopathology studies reveal inflammation of the artery wall with predominance of CD4+ T lymphocytes and macrophages, which frequently undergo granulomatous organization with formation of giant cells. Immunopathology and molecular studies performed with temporal artery biopsies have led to the current pathogenic model [2],

GCA is primarily an immune-mediated disease due to a maladaptive response to endothelial injury, occurring in susceptible individuals and triggered by factors that have not been identified with certainty. Several microbe and viral sequences, including varicella-zoster virus, have been detected in temporal artery lesions, but no convincing causal relationship has been demonstrated [3].

The initial inflammatory response involves the activation of dendritic cells, present in the adventitia of normal arteries, through pathogen- or damage-sensing

receptors, such as toll-like receptors, producing chemokines able to attract and retain dendritic cells as well as lymphocytes and macrophages. Once activated, dendritic cells are enabled to process and present antigens and strongly express major histocompatability complex (MHC) class II and costimulatory molecules (CD83 and CD86) required for T-cell recruitment [4].

Once activated, both T helper (Th)1 and Th17 differentiation pathways contribute to the development of vascular inflammation. Interleukin (IL)-12 and IL-18 produced by dendritic cells stimulate Th1 differentiation and production of interferon (IFN)-gamma which is noticeably expressed in GCA-involved arteries. IFN-gamma causes endothelial cells and vascular smooth muscle to recruit more Th1 cells, CD8+ T cells, and monocytes which differentiate into macrophages and the characteristic giant cells that produce growth factors, interleukins and proteolytic enzymes playing a distinctive role granuloma formation that progressively narrow and obstruct the vessel wall [5].

Moreover, IL-1-beta, IL-6, and IL-21 promote Th17 differentiation, which is maintained by IL-23 and results in IL-17A expression. IL-17A, profusely expressed in GCA lesions, is a proinflammatory cytokine having pleiotropic effects on a variety of cells, namely macrophages, fibroblasts, endothelial cells and vascular smooth muscle cells [6].

Systemic manifestations are related the inflammatory process and cytokine amplification. Inflammation-induced vascular remodeling leads to concentric intimal hyperplasia occurring as a repair mechanism in response to injury of the blood vessel wall. End-organ involvement results from mural hyperplasia which can narrow the arterial lumen, resulting in distal ischemia and ischemic complications of the disease [7].

2. Clinical manifestations of giant cell arteritis

Clinical presentation of GCA tends to be subacute, but may occur over the course of a few days. Although symptoms of GCA are nonspecific, some key findings may strongly suggest this diagnosis. Systemic symptoms are common in GCA and vascular involvement can be widespread, causing stenosis and aneurysm of affected vessels. It is the targeting of the tiny muscular arteries from cranial branches of the aortic arch, however, that gives rise to many of the most characteristic symptoms of GCA. External carotid branch involvement accounts for the high frequency of cranial symptoms [8].

2.1 Constitutional symptoms

Systemic symptoms associated with GCA are frequent and include fever, fatigue, anorexia and weight loss. These symptoms may occur for a few days and may prolong to several weeks. Fever is usually low grade and occurs in up to one-half of patients. It has been stated as well that 1 out of 6 fevers of unknown origin in older adults was due to GCA [9]. About 10% of patients with GCA present with constitutional symptoms and laboratory evidence of inflammation as the only clues to the diagnosis [10]. Thus, in an older adult with fever or constitutional symptoms not explained by an initial evaluation for infection or malignancy, a diagnosis of GCA warrants consideration [11].

2.2 Headache

Headache is a common presentation of GCA, being the initial symptom in 33% of cases and present in about 80% of patients [12]. Importantly, the headache is

either new, in a patient without previous history of headaches, or of a new type in a patient with chronic headache.

While the headache has no pathognomonic features, headaches due to GCA are typically throbbing and continuous, located over the temples, but can also be frontal, occipital, unilateral or generalized. Descriptions of the pain range from a dull or burning sensation to focal tenderness on direct palpation. Patients may note scalp tenderness with hair combing or when wearing a hat. The headache can progressively worsen, wax and wane, or sometimes recede before treatment is started [13].

2.3 Jaw claudication

Jaw claudication results from ischemia of the maxillary artery supplying the masseter muscles and is highly predictive of temporal arteritis. Nearly 50% of patients experience jaw claudication, a symptom consisting of mandibular pain, discomfort or fatigue triggered by mastication or prolonged speaking and relieved by stopping [14]. An analysis of the diagnostic value of temporal artery biopsies, which correlated positive biopsies with clinical symptoms, revealed jaw claudication as the symptom most highly associated with a positive biopsy [15].

In some cases, patients note a trismus-like symptom, with either perceived or actual limitation of temporomandibular joint excursion. Claudication symptoms occasionally affect the tongue, with repeated swallowing and tongue infarction being almost pathognomonic for GCA [16, 17].

2.4 Ocular involvement

The reported incidence of visual symptoms in GCA ranges widely [18]. These include permanent visual loss, transient monocular (and, rarely, binocular) vision impairment, consisting of unilateral visual blurring, vision loss or diplopia. Patients refer an abrupt partial field defect or temporary curtain effect in the field of vision of one eye [19]. It can be useful in the course of evaluating the possible significance of a reported visual disturbance to inquire if the patient tried to cover each eye since explicit monocular visual loss would heighten concern for GCA. Transient visual loss can be a harbinger of permanent visual loss, especially if treatment is not started promptly and thus mandates urgent attention in a patient with suspected GCA.

The most feared complication of GCA is permanent loss of vision, frequently sudden and painless, may be partial or complete, and may be unilateral or bilateral. Permanent loss of vision in GCA results from arteritic anterior ischemic optic neuropathy, central or branch retinal artery occlusion, posterior ischemic optic neuropathy, or, rarely, cerebral ischemia [20]. Even in the current era effective therapy, the incidence of permanent loss of vision ranged from 15 to 20% of patients [20]. Though permanent visual loss may be preceded by single or multiple episodes of transient visual loss, it can also occur with devastating swiftness. When untreated, contralateral eye involvement commonly occurs between the first two weeks after initial onset [21]. With adequate glucocorticoid treatment, if there is no further visual deterioration within the first week, existing vision in affected eye and the vision in the unaffected eye will remain intact, virtually stopping the subsequent risk of sight loss [22].

Extraocular motility disorders occur in approximately 5% of atients and include diplopia which has a high specificity when accompanied by other symptoms suggestive of GCA [23]. Diplopia, which is usually transient, can result from ischemia of any portion of the oculomotor system, including the brainstem, oculomotor nerves, and the extraocular muscles themselves [24].

Although rare, GCA can manifest with Charles Bonnet syndrome, a phenomenon of visual hallucinations in psychologically normal individuals who have visual loss due to lesions in either peripheral or central visual pathways [25].

2.5 Musculoskeletal involvement

GCA is closely linked to polymyalgia rheumatica (PMR) and this well-known association has therapeutic and prognostic consequences. About 40 to 60% of GCA patients have manifestations of PMR, an inflammatory rheumatic condition clinically characterized by symmetrical proximal polyarthralgia and myalgia, with aching and stiffness on shoulders, hip girdle, neck, torso and an unfamiliar sense of fatigue [26].

Less commonly, distal findings can occur, involving synovitis of peripheral joints, especially at the wrists and metacarpophalangeal joints, with distal extremity swelling and pitting edema, known as remitting seronegative symmetrical synovitis with pitting edema (RS3PE) syndrome, puffy edematous hand syndrome or distal extremity swelling with pitting edema [27]. In this syndrome symptoms can appear abruptly, with significant swelling, usually pitting, extending over the dorsal side of the wrists and metacarpophalangeal joints producing a "boxing glove" appearance, and with limited range of motion of the hands and wrists. The term seronegative refers to the absence of antibodies namely rheumatoid factor (RF) and cyclic citrullinated peptide (anti-CCP) for differential diagnosis with rheumatoid arthritis. Imaging with ultrasonography and MRI reveal tenosynovitis of the extensor tendon of the forearms and hands, with less flexor tenosynovitis and synovitis of the metacarpophalangeal and proximal interphalangeal joints [28]. A paraneoplastic association with solid tumors and hematologic disorders has been reported, but in clinical practice such an occurrence is rare [29].

2.6 Large vessel involvement

Involvement of the extracranial branches of the carotid artery is the source of the classic cranial symptoms of GCA. However, besides the carotid arteries, GCA often involves the aorta and its major branches which is designated large vessel (LV) -GCA. The clinical consequences of LV-GCA include aneurysms and dissections of the aorta, particularly the thoracic aorta, as well as stenosis, occlusion, and ectasia of large arteries. This subset of patients with predominantly upper extremity arterial vasculitis, may have variable clinical presentations and diagnostic delay [30].

While symptomatic LV involvement is uncommon, a key point is that subclinical LV-GCA involvement is present in a significant number of patients and can underlie a systemic presentation of GCA without having necessarily cranial symptomatology. Different publications using imaging modalities such as fluorodeoxyglucose positron emission tomography (FDG-PET), computed tomographic (CT) angiography and color-coded duplex ultrasonography have consistently highlighted the involvement of subclavian, axillary, brachial arteries or the thoracic aorta in more than 30% of patients with confirmed GCA diagnosis [31, 32].

Although the disease pattern of LV-GCA differs from cranial GCA, clinical features overlap. Systematic screening of patients with the cranial phenotype can demonstrate large artery involvement. On the other hand, temporal artery biopsies are positive in only approximately one-half of patients with LV GCA, underlining the essential role of imaging for the diagnosis of this phenotype.

In contrast with the cranial phenotype, LV-GCA patients were younger at disease onset (66 vs. 72 years), had longer duration of symptoms prior to the diagnosis (median 3.5 months vs. 2.2 months), fewer cranial symptoms (41% vs. 83%) and were more likely to have arm claudication at presentation (51% vs. 0%) [33].

Aortic aneurysms have been recognized in 10% of cases [34]. The thoracic aorta is more frequently affected than the abdominal aorta, and within the thoracic aorta the descending segment is the main site. It is important to note that in these cases, there is often little or no clinical or laboratory evidence of systemic activity of GCA. When compared with the general population, patients with GCA have a twofold increased risk of aortic aneurysm and this should be considered within the range of other risk factors such as male gender, age or smoking [35]. Histopathologic examination of specimens from surgery or autopsy show fibrosis and different degrees of active aortitis, including giant cells. These findings suggest two mechanisms of disease: chronic recrudescent aortitis causing elastin and collagen disruption, or mechanical stress on an aortic wall weakened in the early active phase of the disease. Aortic dissection or rupture is a rare major complication of aortitis and was identified in 5% of patients with LV-GCA with aortic aneurysm [36]. Involvement of the ascending aorta can lead to aortic rupture, and coronary arteritis may result in myocardial infarction.

GCA can also affect the subclavian arteries distal to the take-off of the vertebral arteries and extend through the axillary arteries to the proximal brachial arteries. On physical examination, arterial bruits, diminished or absent blood pressures and arm claudication can be identified. Cold intolerance of the involved extremity is common, but explicit digital ulcerations and gangrene are rare because of adequate collateral arterial supply. The vessel wall is circumferentially affected, in contrast to the eccentric appearance of atherosclerosis. The descending aorta and mesenteric, renal, iliac, and femoral arteries can less commonly be affected, with attendant complications of intestinal infarction, renal infarction, crural infarction and ischemic mononeuropathies [37]. Clinically evident lower-extremity arterial involvement can occur but is also uncommon [38].

2.7 Central nervous system involvement

Stroke is a rare but important complication of GCA and is typically due to stenosis of carotid and the vertebral or basilar arteries. Even with aggressive steroid and immunosuppressive therapy it is associated with high morbidity and mortality. In descriptive cohorts, the frequency of stroke within the first four weeks of the diagnosis of GCA, and thus construed as potentially disease-related, has ranged from 1.5 to 7.5% [39].

Though strokes due to GCA can occur in the distribution of both the internal carotid and vertebrobasilar arteries, they are noticeably more frequent in the latter location. More than one-half of strokes attributable to GCA occur in the vertebrobasilar system This figure contrasts with population-based studies of transient ischemic attacks and stroke overall, which occur five times more often in the territory of the internal carotid arteries compared with the vertebrobasilar arteries [40]. Arteritic involvement of the vertebral arteries can result in vertigo, ataxia, dysarthria, homonymous hemianopsia, or bilateral cortical blindness. Bilateral vertebral artery involvement, which causes rapidly progressive brainstem or cerebellar neurologic deficits with high mortality, is highly suggestive of GCA.

Peripheral neuropathy, myelopathy, higher cortical dysfunction or dementia, and pachymeningitis are uncommon complications of GCA.

2.8 Respiratory tract symptoms

Patients with GCA can present upper respiratory tract symptoms, in particular a non-productive cough. The cause of cough is unknown, but may result from vasculitis in the area of cough receptors, which are located throughout the

respiratory tree, or vasculitis of the ascending pharyngeal artery, a branch of the external carotid artery. Vasculitis of the bronchial arteries has been observed in the post-mortem examination of a patient with disseminated GCA. Furthermore, involvement of the lungs in GCA has also been reported as cases of interstitial lung disease (ILD) as an uncommon clinical manifestation of GCA [41].

2.9 Cardiac involvement

Patients with GCA are at increased risk for cardiovascular events, but cardiac involvement is rare. Myocardial infarction is an example of serious complication that may arise. Cases of GCA patients developing myocarditis and myopericarditis are uncommon but have been reported [42].

2.10 Head and neck involvement

Branches of the external carotid artery may often be affected in GCA, namely the superficial temporal artery. Jaw claudication results from arteritic involvement of the muscles of mastication (masseter, temporalis, and medial and lateral pterygoid muscles), all of which are supplied by the branches of the external carotid artery. Involvement of other branches of the external carotid artery accounts for many of the other extracranial symptoms that can accompany the presentation of GCA, including: maxillary and dental pain, facial swelling, throat pain, tongue pain and macroglossia [43].

2.11 Atypical features

GCA of the female genital tract was first reported by Ritawa in 1951 [44]. Female genital tract involvement (ovary, fallopian tubes, or uterus) was identified by chance on histopathologic inspection of surgical specimens surgically removed for gynecological reasons unrelated to GCA.

Vasculitis of the breast does occur and should require exclusion of systemic involvement. When constitutional symptoms, especially arthralgia and myalgia, are present and acute phase reactants are elevated, a work-up for systemic disease is especially warranted. Histologic characteristics included vessel size and type of inflammatory infiltrates including foamy macrophages and giant cells [45]. These features did not correlate with disease extent, plus constitutional and musculoskeletal manifestations were usually absent. Patients generally did not require systemic therapy and may be cured by resection alone.

3. Conclusion

GCA should always be considered in the differential diagnosis of a new-onset headache in patients 50 years of age or older with an elevated erythrocyte sedimentation rate. Temporal artery biopsy remains the criterion standard for diagnosis of this granulomatous vasculitis but increasing evidence supports the use of imaging studies such as ultrasonography as a less invasive from of diagnosis.

The onset of symptoms in GCA tends to be subacute, but abrupt presentations occur in some patients. Although systemic manifestations are characteristic of GCA and although vascular involvement can be widespread, clinical manifestations of the disease most frequently result from involvement of the cranial branches of arteries originating from the aortic arch. When taking the patient's history, the clinician must ask about the following types of symptoms: systemic symptoms, such

as fever, fatigue, and weight loss; headache; jaw claudication, which is the symptom most highly predictive of a positive temporal artery for the diagnosis of GCA; visual symptoms, particularly transient monocular visual loss and diplopia. The most threatening complication of GCA, visual loss, is a potential result of the cranial phenotype arteritis.

A close relationship exists between GCA and PMR but the precise nature of this association is poorly understood. Several authors have suggested that these two entities are actually different stages of the same disease process. Symptoms of polymyalgia rheumatica occurring in a patient with GCA include characteristic proximal polyarthralgias and myalgias, sometimes accompanied by remitting seronegative symmetrical synovitis with pitting edema (RS3PE).

Most GCA patients present with clinical manifestations that are the result of vascular involvement but a variable proportion of patients may present without obvious vascular manifestations. Imaging may be particularly helpful in the diagnosis of GCA of large arteries in patients with atypical or occult GCA disease. Subclinical involvement of the aorta and large arteries is frequent, a clinical consequence of which can be aortic aneurysm which rarely can be complicated with dissection or rupture. Measurement of the blood pressures in both arms and careful assessment of the arterial tree by palpation and auscultation should be performed in all patients with suspected GCA. When compared with cranial disease, LV-GCA patients have higher relapse rate, greater corticosteroid requirements and increased prevalence of aortic aneurysm. It should be noted that both the 1990 and the revised 2016 American College of Rheumatology criteria may fail to recognize the LV-GCA phenotype, since a portion of LV-GCA do not have cranial symptoms.

The major risk factor for developing giant cell arteritis is aging. The disease almost never occurs before age 50 years, and its incidence rises steadily thereafter. Giant cell arteritis is a more heterogeneous condition than previously thought. Clear knowledge of all the potential clinical manifestations is essential to avoid a delayed diagnosis and associated complications. Although most of these manifestations occur prior to steroid therapy, they may also develop during the early phase of therapy or relapse with tapering of the dose of steroids. Earlier diagnosis, close monitoring and improving the treatment protocols may prevent mortality and improve morbidity in these cases.

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